1108-70 Is the Relationship Between Left Ventricular Mass and Endothelium-Dependent Vasodilatory Function Independent of Blood Pressure?

Rigobert Lapu-Bula, Rongling Li, Adefisayo Oduwole, Brenda Lankford, Cheryl Pack, Jan Morgan, Nkemdiche Sunday, Jeanette St Vrain, Priscilla Pemu, Elizabeth Ofili, *Morehouse School of Medicine, Atlanta, Georgia.*

Background: Recent studies reported that increased left ventricular mass (LVM) is associated with impaired endothelium-dependent vasodilatory function (EDF). It is unclear, however, whether this relationship is independent of blood pressure (BP) in hypertensives and normotensives. Methods: We therefore evaluated the effects of BP on the relationship between echocardiographic LVM and EDF in 59 African American (AA) hypertensives (49±12 yrs) and 42 AA normotensives (40±11 yrs). LVM was calculated (Devereux formula) and indexed to body surface area (LVMI) to define the presence of LV hypertrophy (LVH) (LVMI >134/110 g/m² for men/women). EDF was assessed as flow-mediated dilation (FMD) of the brachial artery during reactive hyperemia, using high-resolution ultrasound. Results: Compared to normotensives, hypertensives had higher LVMI (105±32 vs. 81±24 g/m², P<0.001) and lower FMD (9±6 vs. 16±6%, P<0.0001). In addition, patients with LVH had a significantly lower FMD than patients without LVH (7±6 vs. 13±7, P<0.001). FMD inversely correlated with LVMI (r =-0.53, P<0.0001), systolic BP (r =-0.45, P<0.0001) and diastolic BP (r =-0.43, P<0.0001). Regression coefficients revealed a negative relation between LVMI and FMD in univariate model (beta= -0.10, P<0.0001) and after adjusting for age, gender, systolic and diastolic BP (beta= -0.05, P<0.05). Conclusion: Impairment of FMD is inversely related to LVM, and this relationship appears to persist but likely attenuated after accounting for the well-known influences of blood pressure.

1108-91 Exercise Blood Pressure Threshold for Left Ventricular Hypertrophy in Normotensive and Hypertensive Middle-Aged Men

Peter Kokkinos, Andreas Pittaras, Athanasios Manolis, Puneet Narayan, Vasilios Papademetriou, *Veterans Affairs Medical Center, Washington, Dist. of Columbia, Georgetown University Medical Center, Washington, Dist. of Columbia.*

Background: An abnormal rise in systolic blood pressure (SBP) during exercise is associated with increased risk for hypertension (HTN) and left ventricular hypertrophy (LVH). However, the magnitude of change in exercise SBP associated with LVH is not well defined.
Methods: We assessed left ventricular structure (echocardiography) and exercise blood pressure (BP) in middle-aged (52±5 yrs) normotensive (n=133) and hypertensive (n=121) men free from heart disease, smoking, and antigypertensive medication, to determine the association between left ventricular structure and exercise BP.
Results: Multiple regression analysis (stepwise) revealed that SBP at 6 minutes of exercise was the strongest predictor of left ventricular mass index (LVMI) for normotensive (R^2= 0.49) and hypertensive men (R^2=0.41). Since LVH was defined as LVMI>116 g/m², we regressed the 6-minute exercise SBP against LVMI for each group. The model revealed that a SBP≥167 mm Hg for normotensive and ≥160 mm Hg for hypertensive men were the minimum SBP levels to yield LVMI values >116 g/m². LVH was present in 71% of normotensive and 90% of the hypertensive men whose SBP met the respective level at 6 minutes of exercise. Furthermore, these men were 6 times more likely to have LVH (Odds Ratio: 6.0; CI:3.6-9.8; p<0.000). Comparisons between those who met or exceeded the respective level of SBP at 6 minutes of exercise and those who did not, revealed higher LVMI values (129±22 g/m² vs 101±14 g/m² ; p=0.000) for normotensive and (144±21 g/m² vs 106±6 g/m²; p=0.000) for hypertensive men respectively.
Conclusions: 1) SBP at 6 minutes of exercise is the strongest predictor of LVH for normotensive and hypertensive middle-aged men; 2) The exercise BP threshold for LVH appears to be a SBP≥167 mm Hg for normotensive and ≥160 mm Hg for hypertensive men achieved at a workload of approximately 7 METs.

1108-92 Electrocardiographic Markers of Cardiac Hypertrophy Show Greater Heritability Than Echocardiographic Left Ventricular Mass: A Family Study

Bongani M. Mayosi, Bernard Keavney, Attila Kardos, Crispin H. Davies, Peter J. Ratcliffe, Martin Farrall, Hugh Watkins, *Department of Cardiovascular Medicine, John Radcliffe Hospital, Oxford, United Kingdom.*

Background: Electrocardiographic and echocardiographic measures of cardiac hypertrophy are independent predictors of cardiovascular morbidity and mortality. There is increasing evidence to show that echocardiographic left ventricular mass is genetically determined, but little is known about the magnitude of genetic determination of electrocardiographic measures of cardiac hypertrophy. We set out to assess the heritability of continuous measures of left ventricular hypertrophy determined by electrocardiography and echocardiography.
Methods: We studied 955 members of 229 Caucasian extended families, ascertained through a hypertensive proband. Electrocardiographic measurements were performed manually on normal resting 12-lead electrocardiograms, and echocardiographic parameters were determined on M-mode images. Sex-specific residuals for left ventricular phenotypes were calculated, adjusted for age, systolic blood pressure, weight, height, waist-hip ratio, and presence of diabetes. Heritability was estimated from familial correlations with adjustment for spouse resemblance, and by using variance components methods with ascertainment correction for proband status.
Results: The heritability estimates (range) were higher for Sokolow-Lyon voltage (39-41%) and RaVL voltage (30-31%) than for echocardiographic left ventricular mass (23-29%). Cornell voltage, Cornell product, and electrocardiographic left ventricular mass had heritability estimates of 19-25%, 28-32%, and 12-18%, respectively.
Conclusions: The greater heritability of Sokolow Lyon voltage and RaVL voltage suggests that electrocardiographic phenotypes may be particularly important for the molecular investigation of the genetic susceptibility to cardiac hypertrophy. Finding genes that influence the electrocardiographic markers could help unravel the pathophysiology of cardiac hypertrophy and lead to improvements in prevention, diagnosis, and treatment of at-risk populations.

1108-93 Is Urinary Albumin Excretion an Independent Predictor of Cardiovascular Mortality in Patients With Electrocardiographic Left Ventricular Hypertrophy? The LIFE Study

Kristian Wachtell, Michael H. Olsen, Björn Dahlöf, Richard B. Devereux, Stevo Julius, Sverre E. Kjeldsen, Markku S. Nieminen, Peter M. Okin, Knut Borch-Johnsen, Hans Ibsen, *Glostrup Univeristy Hospital, Glostrup, Denmark, Weill Medical College of Cornell University, New York, New York.*

Background: Recently, we found that increased urine albumin/creatinine ratio (UACR) as well as electrocardiographic (ECG) left ventricular hypertrophy (LVH) were related to high blood pressure (BP) in hypertensive patients independent of age, smoking, prevalence of diabetes, suggesting parallel BP-induced cardiac hypertrophy and renal glomerular permeabilty. However, it is not clear whether this predicts an independent effect on mortality.
Methods: ECG and morning spot urine were obtained in 8,165 patients with stage I-III hypertension and ECG LVH (Cornell voltage-duration or Sokolow-Lyon voltage criteria) after 14 days placebo treatment. Renal glomerular permeability was evaluated by UACR and was defined as micro- or macroalbuminuria if >3.5 or 35 mg/mol, respectively.
Results: During 68 [95% CI 67-69] months 592 (6%) deaths occurred. Of these 317 (3.9%) were cardiovascular (CV) deaths, which plus non-fatal myocardial infarction and stroke compressed the composite primary CV end-point (n=888, 10.9%). Patients with either micro- or macroalbuminuria had on average 1.7 or 4.3-fold higher CV mortality rate, respectively, compared to normoalbuminuric patients. Similar micro- or macroalbuminuria groups had 1.8 or 2.6-fold higher rates of composite end-point compared to normoalbuminuric patients. CV mortality rate and composite CV end-point rate increased 8- and 9-fold in patients with macroalbuminuria and LVH by both criteria as compared to normoalbuminuric patients without LVH by either criterion (all p<0.001). When divided into quartiles a striking increase in CV end-points was seen in the 3rd quartile with UACR-values between 1.3-3.9 g/mmol. Cox regression analysis showed that UACR predicts CV mortality and composite CV end points independent of LVH, systolic BP, age, sex, diabetes and smoking.
Conclusion: UACR is an independent predictor of CV morbidity and mortality, even after taking into account baseline ECG LVH and other CV risk factors. The presence of cardiac end-organ damage and albuminuria potentiates the risk of overall mortality. Furthermore, the threshold-limit for microalbuminuria in patients with hypertension and LVH should be reduced to no more than 1.0 mg/mmol.

1108-94 Increased Expression of Type-2A and Type-2B Protein Phosphatases During the Development of Left Ventricular Hypertrophy

Ramesh C. Gupta, Sudhish Mishra, Nivedita Tiwari, Hani N. Sabbah, *Henry Ford Health System, Detroit, Michigan.*

Background: Type-2B protein phosphatase (PP2B) is implicated in the development of LV hypertrophy (LVH). The role of type-2A protein phosphatase (PP2A) in LVH, however, is not known. We tested the hypothesis that both PP2A and PP2B are involved in the LVH.
Methods: Expression of the catalytic subunit of PP2A (PP2Ac) and PP2B (PP2Bc) was examined by Western blots in SDS-extract of LV myocardium obtained from Lewis rats (n=18) in which LVH was produced using one kidney-one clip (1K1C) and in sham-operated rats (n=18). Six rats from each group were sacrificed at 1, 4, and 8 weeks thereafter. LV weight to body weight (LVW/BW) ratio was used to index of LVH. Western blots were quantified in densitometric units and the data expressed as percent change from sham values.
Results: 1K1C rats developed LVH as early as week 1 post-operatively and the extent of LVH increased progressively thereafter. In LVH rats, PP2Bc but not PP2Ac expression increased at week 1. Expression of both PP2Ac and PP2Bc, however, increased significantly at 4 weeks and 8 weeks compared to sham. Both PP2Ac and PP2Bc were lower at week 8 compared to week 4 (data in table).
Conclusions: The results suggest that increased expression of PP2Bc is associated with initiation and progression of LVH. Increased expression of PP2Ac follows at a later stage of LVH and may play a role in its progression. These temporal differences in the expression of PP2Ac and PP2Bc represent therapeutic opportunities to interfere with the LVH process at different stages of its evolution.

	LVW/BW (%)	PP2Ac (%)	PP2Bc(%)
Week 1	117 ± 4	100 ± 7	253 ± 18
Week 4	135 ± 5	255 ± 26*	314 ± 11*
Week 8	186 ± 6*^	142 ± 15*^	183 ± 8*^

*=P<0.05 vs Week 1; ^=P<0.05 vs. Week 4

1108-95 Older Women With Mild Hypertension Have Higher Left Ventricular Mass Than Men After Adjustment for Lean Body Mass

Jidong Sung, Anita C. Bacher, Katherine L. Turner, Jamie R. DeRegis, Paul S. Hees, Edward P. Shapiro, Kerry J. Stewart, *Johns Hopkins University School of Medicine, Baltimore, Maryland.*

Background: When left ventricular mass (LVM) is indexed by measures of body size, such as body surface area (BSA) and height, gender difference persist with men having a higher LVM index. Recent studies suggest that LVM indexed by lean body mass (LBM) may eliminate the gender difference seen in general populations. With the novel techniques for

assessing body composition and LVM, we examined the gender difference of LVM adjusted for LBM in older persons with mild hypertension.
Method: Fifty-two subjects (22 men and 30 women) with untreated mild hypertension, aged 55 to 75 years, and otherwise healthy, were examined. Resting BP was obtained at 4 or 5 visits at least 1 week apart and averaged. Body composition was assessed using dual energy X-ray absorptiometry. LVM was determined from MRI and was indexed by BSA, height, height$^{2.7}$ and LBM.
Results: There were no gender differences in age, SBP and BMI. Men had higher mean BP, unindexed LVM, and LBM than women. Fat mass and percent body fat were higher in women compared to men. Unlike the LVM indexed by other measures, LVM indexed by LBM was greater in women than men, as shown in table. In a multiple regression model, gender was a predictor of LVM after adjustment for LBM, mean BP, percent body fat and LBM - gender interaction (adjusted means, female vs. male, 135 ± 8 g vs. 109 ± 12 g, $p < 0.05$)
Conclusion: In this population of older persons with mild hypertension, women had a higher LVM relative to their lean body size, suggesting that women may be more susceptible to LVH than men.

Table * $p < 0.01$, ** $p < 0.05$, male vs. female

LVM indexed by	BSA**	Height*	Height$^{2.7}$	LBM**
Male	73 ± 16 g/m^2	89 ± 21 g/m	33 ± 7 g/m$^{2.7}$	2.68 ± 0.52 g/kg
Female	64 ± 13 g/m^2	75 ± 13 g/m	33 ± 6 g/ m$^{2.7}$	3.07 ± 0.60 g/kg

1108-96 **Arterial Stiffness and Left Ventricular Geometry and Function in Hypertensive Patients With Electrocardiographic Left Ventricular Hypertrophy: The LIFE Study**

Vittorio Palmieri, Jonathan N. Bella, Mary J. Roman, Eva Gerdts, Vasilios Papademetriou, Kristian Wachtell, Markku S. Nieminen, Björn Dahlöf, Richard B. Devereux, *Weill Medical College of Cornell University, New York, New York.*

Background: Arterial stiffness can be assessed by the ratio pulse pressure (PP) over echocardiographic stroke volume (SV). We evaluated relations of arterial stiffness to left ventricular (LV) geometry and function in hypertensive patients with electrocardiographic (ECG) LV hypertrophy (H).
Methods: Of participants in the echo-substudy of the Losartan Intervention For Endpoint (LIFE) reduction in hypertension study, selected to have ECG-LVH by Cornell voltage-duration product or Sokolow-Lyon voltage criteria, no heart failure or severe aortic stenosis, we identified 858 subjects (88%, 66±7 yrs/old) with PP/SV available. The study sample was divided in tertiles of PP/SV (cutpoints: 0.86 and 1.11 mm Hg/ml). M-mode and Doppler SV were averaged.
Results: With higher PP/SV, age, proportions of women and diabetics, and systolic blood pressure (BP) were higher (all $p<0.01$); diastolic BP, body height and weight, and SV were lower (all $p<0.01$). Mean BP, total/HDL cholesterol, urinary albumin/creatinine and proportion of wall motion abnormalities were similar in tertiles of PP/SV. After adjusting for age, gender and body surface area, LV mass and LV internal diameter were lower while relative wall thickness (RWT=LV concentricity) was higher with higher PP/SV (all $p<0.01$); ejection fraction was similar across tertiles ($p>0.5$) while stress-corrected midwall shortening (scMWS) was lower with higher PP/SV ($p<0.01$). After adjustment for age and gender, LV filling parameters and heart rate were similar in tertiles of PP/SV (all $p>0.1$). In multivariate models, independent correlates of PP/SV were older age, lower body weight, female-gender and diabetes ($R=0.48$, $p<0.001$); higher RWT was related to higher PP/SV independent of age, gender, and mean BP ($R=0.30$, $p<0.001$); higher LV mass was independently predicted by higher SV, male-gender, higher body weight, older age and higher mean BP, but not PP ($R=0.64$, $p<0.001$); PP/SV was not related to scMWS independent of RWT.
Conclusions: In elderly hypertensives with ECG-LVH, higher arterial stiffness is related to concentric LV geometry, which may offset afterload and preserve LV chamber function, but is associated with impaired myocardial function.

FEATURED ORAL PRESENTATION

825FO Featured Oral Session...Current Topics on Hormonal Replacement Therapy

Monday, March 18, 2002, 2:00 p.m.-3:30 p.m.
Georgia World Congress Center, Room 160W

2:15 p.m.

825FO-2 **Addition of Statin Attenuates the Increase in C-Reactive Protein During Estrogen Replacement Therapy in Postmenopausal Women**

Kwang K. Koh, Gyorgy Csako, William Schenke, Richard O. Cannon, III, *NHLBI, Bethesda, Maryland.*

Background: Randomized clinical trials have shown that HMG-CoA reductase inhibitor (statin) therapy reduces cardiovascular risk, the mechanism of which may include diminished arterial inflammation as evidenced by reduction in levels of C-reactive protein (CRP) in serum. Because estrogen replacement therapy increases CRP in postmenopausal women, which could have pro-inflammatory consequences and compromise any benefit to cardiovascular risk, we determined whether the addition of statin might modify the estrogenic effect on CRP. **Methods:** In a double blind, 3-period crossover study, we randomly assigned 28 healthy postmenopausal women to conjugated equine estrogens (CEE) 0.625 mg, simvastatin 10 mg, and their combination daily for 6 weeks, with each treatment period separated by 6 weeks off drugs. CRP was measured by high sensitivity immunometric assay (sensitivity 0.01mg/dL) before and after 6 weeks of each treatment. **Results:** CEE increased CRP from 0.37 ± 0.06 to 0.65 ± 0.13 mg/dL, simvastatin decreased CRP from 0.37 ± 0.06 to 0.33 ± 0.05 mg/dL, and the therapies combined increased CRP from 0.38 ± 0.08 to 0.48 ± 0.08 mg/dL (all $P<0.02$ vs. respective baseline values), with significant differences in changes in CRP levels among these therapies ($P<0.05$ by ANOVA). Post-hoc testing showed that the 29 ± 8 % increase in CRP on the combination of CEE with simvastatin was significantly less than the 89 ± 32 % increase in CRP on CEE alone ($P<0.01$). The effect of combination therapy on CRP did not correlate with baseline CRP, or with baseline or treatment-induced changes in levels of LDL cholesterol, HDL cholesterol, interleukin-6, or brachial artery flow-mediated dilation as a measure of nitric oxide bioactivity (all $r<0.32$). **Conclusion:** The combination of statin with estrogen therapy may attenuate the potential proinflammatory effect of estrogen administration to postmenopausal women, and maximize any benefit of hormone replacement therapy to cardiovascular risk.

2:30 p.m.

825FO-3 **The Differential Effects of Hormone Replacement Therapy and Selective Estrogen Receptor Modulator on Endothelial Function Seem Related to an Effect on Plasma Asymmetric Dimethylarginine, an Inhibitor of Nitric Oxide Synthase**

Giuseppe Mercuro, Massimo Fini, Cristiana Vitale, Otavio Gebara, Sandra Zoncu, Mauricio Wajngarten, Antonello Silvestri, Paola Rossini, José Antonio F. Ramires, Giuseppe M. Rosano, *San Raffaele Hospital, Roma, Italy, University of Cagliary, Cagliary, Italy.*

Background: Hormone replacement therapy (HRT) improves endothelial function in postmenopausal women. Although in vitro animal studies suggest that the selective estrogen receptor modulator, raloxifene (R), improves endothelial function, its effect in women has yielded conflicting results. One mechanism by which HRT may reverse endothelial dysfunction and increase NO bioavailability is by lowering asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide (NO) synthase. The aim of this study was to evaluate endothelial function and plasma ADMA with HRT or R.
Methods: Brachial artery diameter, endothelium-dependent flow-mediated vasodilation (FMD) of the brachial artery, and plasma levels of nitrite, nitrate, endothelin-1 and ADMA were measured in 20 postmenopausal women with increased cardiovascular risk, treated with either HRT (0.625 conjugated equine estrogens and 2.5 mg medroxyprogesterone acetate) or R (60 mg) for 4 weeks in a double-blind, single cross-over study.
Results: Baseline brachial artery diameters remained unchanged after each treatment phase. FMD significantly improved with HRT but not with R. ADMA significantly decreased with HRT, while a trend towards increased plasma ADMA levels was noted with R.
Conclusions: HRT improves endothelial function in postmenopausal women at risk of cardiovascular disease, which may be due, at least in part, to a reduction in ADMA. In contrast, R seems to increase plasma ADMA, which may negatively affect endothelial function.

	Baseline	HRT	R
FMD (%)	7.4±0.5	12.4±0.6**	6.1±2.0
ADMA	0.76±0.51	0.68±0.63**	0.80±0.65
Nitrite+nitrate (Nox)	41.1±10.3	47.3±8.4*	38.8±6.8
Endothelin-1 (pg/ml)	3.2±0.6	2.8±0.6*	3.2±0.7

*=p<0.05; **=p<0.01, compared to baseline

2:45 p.m.

825FO-4 **Hormone Replacement Therapy and Risk of Myocardial Infarction in Women With Diabetes**

Apoor S. Gami, R. Scott Wright, Sharonne E. Hayes, Stephen L. Kopecky, *Mayo Clinic, Rochester, Minnesota.*

Background: The effect of hormone replacement therapy (HRT) on coronary heart disease (CHD) in postmenopausal women is controversial. Women with diabetes are at markedly increased risk of CHD, yet data on HRT in this population is scarce. The purpose of this study is to describe the effect of HRT on risk of MI in postmenopausal women with diabetes.
Methods: We conducted a case-control study in which case subjects (n = 99) were consecutive postmenopausal women with diabetes admitted to our institution from 1998 to 2000 with a principal diagnosis of MI. Control subjects (n = 306), matched in a 3:1 ratio by age and admission year, were postmenopausal women with diabetes admitted with principal diagnoses other than MI. Medical records were reviewed for demographics, medical history including diabetes complications, CHD risk factors, laboratory data, and current medications. Differences between case and control groups were assessed by the two-sample T-test for continuous variables and the chi-square test for dichotomous variables. The odds ratio, adjusted for group differences by logistic regression models, was used to estimate the relative risk of incident MI for HRT users.
Results: Case and control subjects were of similar age (73 years), height (157 cm), and weight (77 kg). Case and control groups had similar frequencies of hypertension (73%) and active cigarette use (8%). Frequencies of use of insulin (53%), oral hypoglycemic agents (36%), aspirin (46%), and statins (22%) were similar. Frequencies of diabetic retinopathy (19%), neuropathy (21%), and nephropathy (32%) were similar. Average levels of hemoglobin A1c (8.6%) and creatinine (1.7 mg/dl) were similar. More case subjects had previous MI (29% vs. 17%, p = 0.01) and hypercholesterolemia (52% vs. 39%, p = 0.02). Current users of estrogen (with or without progesterone) comprised 16% of case and 15% of control subjects. The relative risk of incident MI for current HRT users was 0.92 (95% CI 0.44 - 1.94).